View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

Eur J Vasc Endovasc Surg (2015) 49, 366—374

Long-term Results of a Randomized Controlled Trial Analyzing the Role of Systematic Pre-operative Coronary Angiography before Elective Carotid Endarterectomy in Patients with Asymptomatic Coronary Artery Disease☆

G. Illuminati [a,e], F. Schneider [b,e], C. Greco [c], E. Mangieri [c], M. Schiariti [c], G. Tanzilli [c], F. Barillà [c], V. Paravati [c], G. Pizzardi [a], F. Calio' [a], F. Miraldi [c], F. Macrina [c], M. Totaro [c], E. Greco [c], G. Mazzesi [c], L. Tritapepe [c], M. Toscano [c], F. Vietri [a], N. Meyer [d], J.-B. Ricco [b,*]

[a] F. Durante Department of Surgical Sciences, University La Sapienza, Rome, Italy
[b] Department of Vascular Surgery, University of Poitiers, Poitiers, France
[c] Department of Cardiology and Cardiac Surgery, University La Sapienza, Rome, Italy
[d] Department of Public Health — GMRC, FMTS, University Hospital of Strasbourg, France

WHAT THIS PAPER ADDS

This study demonstrates that systematic pre-operative coronary angiography, followed by selective myocardial revascularization prior to carotid endarterectomy (CEA), reduces the incidence of late myocardial infarction and increases the survival rate in patients without any previous history of coronary artery disease. Therefore in the future, routine coronary screening should be considered as part of the standard pre-operative cardiac workup for CEA candidates. In addition, considering not only the potential risk of myocardial infarction in these patients but also the opportunity cost entailed, a possibly less invasive screening test with pre-operative thallium scanning or coronary CT should be thoroughly investigated.

Objectives: To evaluate the potential benefit of systematic preoperative coronary-artery angiography followed by selective coronary-artery revascularization on the incidence of myocardial infarction (MI) in patients undergoing carotid endarterectomy (CEA) without a previous history of coronary artery disease (CAD).
Methods: We randomised 426 patients who were candidates for CEA, with no history of CAD, a normal electrocardiogram (ECG), and a normal cardiac ultrasound. In group A ($n = 216$) all patients underwent coronary angiography before CEA. In group B ($n = 210$) CEA was performed without coronary angiography. Patients were not blinded for relevant assessments during follow-up. Primary end-point was the occurrence of MI at 3.5 years. The secondary end-point was the overall survival rate. Median length of follow-up was 6.2 years.
Results: In group A, coronary angiography revealed significant coronary artery stenosis in 68 patients (31.5%). Among them, 66 underwent percutaneous Intervention (PCI) prior to CEA and 2 received combined CEA and coronary-artery bypass grafting (CABG). Postoperatively, no MI was observed in group A, whereas 6 MI occurred in group B, one of which was fatal ($p = .01$).
During the study period, 3 MI occurred in group A (1.4%) and 33 were observed in group B (15.7%), 6 of which were fatal. The Cox model demonstrated a reduced risk of MI for patients in group A receiving coronary angiography (HR,.078; 95% CI, 0.024-0.256; $p < .001$). In addition, patients with diabetes and patients <70 years presented with an increased risk of MI. Survival analysis at 6 years by Kaplan-Meier estimates was $95.6 \pm 3.2\%$ in Group A and $89.7 \pm 3.7\%$ in group B (Log Rank = 6.54, $p = .01$).
Conclusions: In asymptomatic coronary-artery patients, systematic coronary angiography prior to CEA followed by selective PCI or CABG significantly reduces the incidence of late MI and increases long-term survival. **(*ClinicalTrials.gov number, NCT02260453*).**
© 2015 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.
Article history: Received 5 July 2014, Accepted 22 December 2014, Available online 18 February 2015
Keywords: Coronary angiography, Carotid endarterectomy, Pre-operative cardiac workup

☆ Presented at the 29th Annual Meeting of the French Society for Vascular Surgery, Bordeaux, France, 20—23 June, 2014.
[e] GI and FS participated equally and share co-first authorship.
* Corresponding author. J.-B. Ricco, Department of Vascular Surgery, University of Poitiers, Hospital Jean Bernard, 86021, Poitiers, France.
E-mail address: jeanbaptistericco@gmail.com (J.-B. Ricco).
1078-5884/© 2015 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejvs.2014.12.030

INTRODUCTION

The prevalence of coronary artery disease (CAD) among patients undergoing elective vascular surgery has been reported to be between 46% and 71%[1,2] with post-operative coronary complications observed in around 20% of cases[3] and an incidence of cardiac death at 1 year between 6 to 10%.[4–7] In addition, a large retrospective study[8] has shown that coronary artery bypass grafting (CABG) before peripheral vascular surgery improves long-term outcomes.

Panels of experts have recommended CABG before peripheral vascular surgery in patients with unstable angina for whom CABG offers long-term survival benefit.[9] But despite the existence of consensus guidelines, the optimal strategy for pre-operative cardiac risk management among patients scheduled for peripheral vascular surgery remains controversial with the likelihood of discordance between two cardiologists around 54%, and a 26% chance that recommendations for coronary revascularization will be directly contradictory.[10] While some studies have demonstrated the efficacy of coronary angiography or thallium scanning followed by selective coronary revascularization in the prevention of post-operative myocardial ischemia,[11–13] other studies have not only failed to show any substantial benefit but also raised concern about the risk of peri-operative bleeding in conjunction with the dual antiplatelet regimen required after pre-operative percutaneous intervention (PCI).[14–16]

In a previous data analysis, it was demonstrated that systematic pre-operative angiography, followed by selective coronary revascularization, significantly reduced the incidence of post-operative MI after carotid endarterectomy (CEA) in patients without clinical evidence of CAD.[17] We are reporting in the present study, the long-term follow up of this trial to assess whether the systematic use of pre-operative coronary angiography followed by selective coronary artery revascularization significantly reduces occurrence of late MI and improves survival in patients without a previous history of CAD at the time of carotid surgery.

MATERIAL AND METHODS

Study design

This randomized controlled trial (RCT) was conducted between January 2005 and December 2008 at two academic surgical centers and one affiliated surgical service. 426 patients were enrolled in the study. Among them, 216 were randomized to undergo pre-operative coronary angiography (group A) prior to CEA, and 210 underwent CEA without prior coronary angiography (group B) The trial was registered (ClinicalTrials.gov number, NCT02260453) and supported by a grant from the University of Rome. The institutional review board of the University approved the trial protocol and all patients provided written informed consent.

Randomization

Random assignment of patients to the two treatment groups was done independently of participating centers in a one to one ratio. The randomization sequence was generated by a computer program and centralized. The time of randomization was considered as time 0.

Eligibility criteria

The indication for CEA included carotid artery stenosis $>$ 60% according to the NASCET criteria.[18] As previously reported,[17] patients referred for CEA were enrolled in the study if they had no evidence of CAD, defined as the absence of any clinical sign or history of ischaemic cardiac disease, no electrical signs of cardiac ischemia at rest and a left ventricular ejection fraction $>$ 50% on transthoracic echocardiogram. In order to measure functional capacity (METS-metabolic equivalent), the cardiologists included a questionnaire on physical activity following the International Physical Activity Questionnaire (IPQ), the Physical Activity Scale for the Elderly (PASE), and the Metabolic Equivalent Task Scale (METS) with careful investigation of any clinical metabolic impairment before randomization. The items included were (a) classification of effort dyspnea during daily activity, (b) cycling (if adequate), (c) climbing a flight of stairs, (d) walking 4 mph, (e) yard work and other physical activity corresponding to a functional capacity classification of 4–7 METS. All patients presenting with doubtful clinical status and a functional capacity below 4 METS despite a normal left ventricular ejection fraction (LVEF) were excluded from randomization and received a complete coronary workup. Randomized patients had a median METS of 5.8 (4.5–7.6).

In addition, the initial METS classes of patients with positive coronary angiography in group A or without coronary angiography (group B) but presenting with a MI during follow up were not different from those of patients with negative coronary angiography and/or uneventful coronary follow up. As shown in the CONSORT flowchart (Fig. 1) patients were randomized in two groups. In group A, coronary artery stenosis was considered significant if $>$ 75% in diameter reduction as seen on coronary angiography, with the help of intravascular ultrasound in nine doubtful cases. Significant stenosis was treated either by PCI or by CABG according to current treatment standards. After coronary angiography and PCI all patients had ECG monitoring and their serum troponin level was assessed at 4, 8, 12, and 24 hours after the procedure. Peri-procedural MI was defined as electrical changes associated with rise of troponin levels (Table 1). In group B ($n = 210$) patients received CEA without any further cardiac evaluation.

Study endpoint

The primary endpoint of the study was the occurrence of MI at 3.5 years. The secondary endpoint was overall survival and freedom from stroke, along with any complication related to coronary angiography and PCI. These endpoints were evaluated at 30 days and at 6 years from randomization.

Sample size

As previously reported in the CARP (Coronary Artery Revascularization Prophylaxis) trial,[3] MI was observed in approximately 20% of patients after major peripheral vascular surgery. In this study two groups of $>$ 200 patients

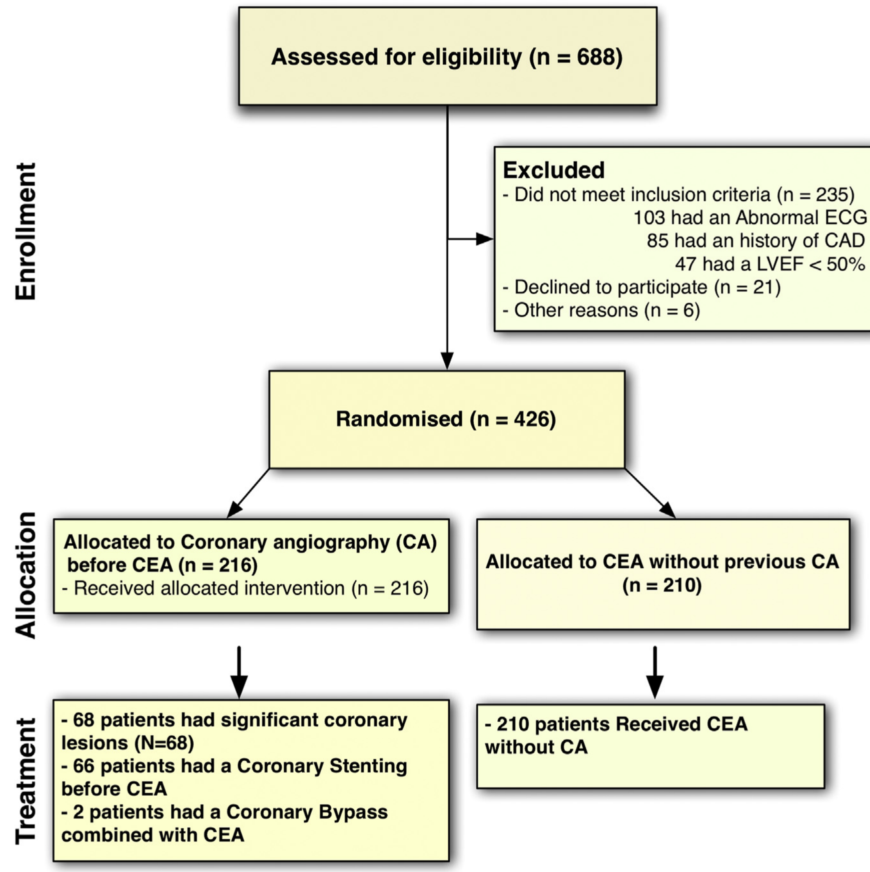


Figure 1. CONSORT flow chart of the study. 688 patients were assessed for eligibility and 426 were randomized in the study (62%). 216 patients were allocated to group A and received CA before CEA. In group B, 210 patients were allocated to CEA without CA. There was no crossover. In group A, 68 patients presented with significant coronary artery disease and received coronary revascularization before CEA. CA = coronary angiography; CAD = coronary artery disease; CEA = carotid endarterectomy.

were enrolled with the hypothesis of a MI reduction rate of 10% in the group with systematic coronary angiography at 3.5 years. With its sample consisting in 400 patients, the study had a 80% power to detect differences in the 3.5 year rates for MI of 20% in one group and 10% in the other group at a significance level $< .05$.

Outcomes

The study was conducted between January 2005 and December 2008. After PCI, patients in group A underwent CEA under dual oral antiplatelet regimen consisting of 100 mg/day aspirin and 75 mg/day clopidogrel. Patients

Table 1. Definitions.

Myocardial infarction	Acute myocardial infarction (MI) was defined by a rise of cardiac troponin with at least one value above the 99th percentile upper reference limit and with at least one of the following:
	(1) New significant ST segment T-wave (ST-T) changes or new left bundle branch block (LBBB)
	(2) Development of pathological Q waves in the ECG
	(3) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, including identification of an intra-coronary thrombus by angiography or autopsy. Percutaneous coronary intervention related myocardial infarction was arbitrarily defined by elevation of cardiac troponin values ($>5 \times$ 99th percentile) in patients with normal baseline values or a rise of cardiac troponin values $>20\%$ if the baseline values are elevated.
	During follow up, if the patient was seen at a distance from the acute onset, any of the following criteria meets the diagnosis for prior myocardial infarction:
	(i) pathological Q waves with or without symptoms in the absence of non-ischemic causes
	(ii) imaging evidence of a region of loss of viable myocardium
Cerebrovascular accident	Any new episode of transient ischemic attack or stroke

who were candidates for CABG underwent combined CEA/CABG and received low molecular weight heparin during the peri-operative period. The remaining patients without PCI or CABG underwent CEA under single oral antiplatelet regimen consisting of 100 mg/day oral aspirin. All patients in both groups received 40 mg/day oral atorvastatin, beginning one week before CEA. In addition, 141 patients (65%) in group A, and 152 patients (72%) in group B received beta blockers for the treatment of hypertension, which was defined as a composite variable including blood pressure values, history of hypertension, and specific medications given for this indication. Hyperlipidemia was defined according to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines, as cholesterol level $>$ 240 mg/dL and/or triglyceride level $>$ 150 mg/dL. At discharge from hospital, in order to eliminate any possible bias related to specific medical treatment, all patients, irrespective of whether or not they were treated by PCI, received a life-long, dual, oral daily antiplatelet regimen consisting of 100 mg of aspirin and 75 mg of clopidogrel. Atorvastatin (40 mg/day) was likewise prescribed to all patients, whereas beta blockers were confirmed in 65% of the patients in group A, and in 72% of the patients in group B. Characteristics of the patients, indications for CEA, and details of the previously reported surgical technique[17] are summarized in Table 2. Among the 216 patients in group A, 68 patients (38.5%) had asymptomatic significant stenosis of the coronary arteries and 66 underwent PCI, 1–8 days prior to CEA, whereas two patients underwent combined CEA and CABG.

Table 2. Characteristics of patients randomized to systematic coronary angiography prior to carotid endarterectomy in group A or direct CEA in group B.

Baseline characteristics	Group A N = 216	Group B N = 210	p value
Age, years ± SD	77 ± 7	74 ± 7	.79
Men (%)	140 (65)	143 (68)	.60
Hypertension (%)	164 (76)	168 (80)	.90
Active smokers (%)	86 (40)	90 (43)	.62
Hyperlipidemia (%)	63 (29)	55 (26)	.52
Diabetes (%)	52 (24)	46 (22)	.73
Lower limb occlusive disease (%)	22 (10)	17 (8)	.40
Chronic renal insufficiency (%)	9 (4)	10 (5)	.82
CAD[a] in Group A			
1-vessel disease (%)	43 (20)		
2-vessel disease (%)	19 (9)		
3-vessel disease (%)	3 (1.5)		
Left main disease (%)	3 (1.5)		
Indications for carotid surgery			
Asymptomatic	157 (72)	151 (71)	
TIA & Stroke	59 (28)	59 (28)	.56
Operative technique			
CEA with patch closure	177 (82)	176 (84)	
CEA by eversion	39 (18)	34 (16)	.76
Carotid Shunt	26 (12)	19 (9)	.27
Duration (minutes ± SD)	126 ± 42	112 ± 36	.82

Characteristics of patients in Group A with preoperative coronary angiography prior to carotid surgery and in Group B without coronary angiography prior to carotid surgery.

CEA: carotid endarterectomy, SD: standard deviation.

[a] CAD: Coronary Artery Disease, lesions seen at systematic coronary angiography in 68 patients of Group A. These lesions were treated before carotid surgery by coronary angioplasty and stenting (PCI) in 66 patients and by coronary artery bypass grafting (CABG) in 2 patients.

Post-operatively and during follow up the diagnosis of MI was confirmed by the occurrence of specific abnormalities on the ECG that were consistent with myocardial ischemia associated with significant elevation of serum troponin level. The diagnosis was eventually further confirmed by thallium myocardial scanning and/or coronary angiography. Neither electrical changes alone, without elevation of serum troponin level, nor isolated serum troponin elevation without MI related specific ECG changes, was considered sufficient for the diagnosis of MI. Myocardial related mortality were defined as any death related to MI collected from the medical records according to the above mentioned definitions. In case of post-operative death, in addition to the electrical changes coupled with serum troponin levels, diagnosis was confirmed at post mortem examination in all cases.

Follow up

Patients were examined in the outpatient clinic every 6 months with a duplex ultrasound of the vessels to the head so as to assess the patency of the carotid revascularization and the status of the contralateral internal carotid artery. Compliance with statin therapy with lipidemia control, smoking cessation and blood pressure control were similarly assessed at this time, and continued to be assessed by the caring physician and cardiologists. Close surveillance of the patients' pillboxes was maintained so as to be sure that they were actually taking their prescribed medicine. This was made possible with the help of the family doctor, who received a summary of the study and a form to fill out regarding compliance with the medical treatment. In parallel, a coronary evaluation was carried out and all symptoms of coronary artery disease were recorded. Medical records of intercurrent hospitalization for any cause were also analyzed. When patients missed the scheduled follow up appointments, relevant information was gathered through exchanges with relatives, caring physicians and cardiologists. Median follow up was 6.2 years (95% CI, 6.1–6.3 years).

Statistical methods

Descriptive statistics were calculated using two sided *t* tests, while chi-square (Pearson and Fisher) tests evaluated differences in patient demographics and co-morbidities between treatment groups. Since the incidence of MI from non-significant coronary artery stenoses has been estimated to be 11.6% at 3.5 years,[19] a follow up period of 3–6 years was taken into consideration. Intention to treat analysis provided information about survival from the time of randomization. Survival curves were generated with the Kaplan–Meier product limit estimates and intergroup differences were evaluated by the log-rank test. The Cox proportional hazards model was used to calculate estimates of relative risk (hazard ratio [HR]) and 95% confidence interval (CI) comparing groups A and B controlling for nine independent variables (age, sex, hyperlipidemia, diabetes, hypertension, peripheral occlusive arterial disease, smoking, previous cerebrovascular accidents, and coronary angiography). Partial likelihood ratio test was used to fit the best model for multivariable Cox regression analysis. All statistical analyses were carried out using SPSS v.22 (IBM corporation). Statistical significance was defined as $p < .05$.

RESULTS

Primary endpoint: hazard ratio for myocardial infarction

Cox proportional hazard model was performed to assess the impact of a number of factors on the likelihood of patients presenting an MI (Table 3). The Cox model demonstrated a significant trend towards reduced risk of MI for patients in group A receiving a pre-operative coronary angiogram compared to those in group B who were operated on without coronary angiography (HR, 078; 95% CI, 0.024—0.256; $p < .001$). In addition, patients with diabetes and patients aged less than 70 years presented with an increased risk of MI with an HR of 2.86 (95% CI, 1.46—5.60; $p = .002$) for diabetics versus non-diabetics and an HR of 4.02 (95% CI, 2.03—7.98; $p < .001$) for patients aged less than 70 years versus older patients (Fig. 2).

During the study period, three MIs (2 non-STEMI, 1 STEMI) occurred in group A (1.4%), and 33 MI (18 non-STEMI, 15 STEMI) in group B (15.7%; $p < .001$). No MI was observed within 30 days of CEA in group A versus 9 MIs of which one was fatal in group B ($p = .01$). In group A, all three MIs were delayed at 22, 59, and 63 months after randomization, one MI was due to restenosis of a PCI performed before CEA, and two MIs occurred in patients who presented a non-significant coronary artery stenosis at the time of CEA. None of these three late MIs was fatal, and related coronary artery lesions were treated by PCI.

Overall, 33 MIs were observed in group B (15.7%) of which six were fatal, while the other 27 were managed by either PCI ($n = 18$), CABG ($n = 2$), or medical treatment alone due to non-reconstructible CAD ($n = 7$).

Compliance was assessed for the statin and dual antiplatelet regimens and was comparable in both groups. For statins, at 6 year follow up compliance was 84% (n = 136) in group A vs. 81% (n = 129) in group B, ($p = .88$). For dual antiplatelet regimens, compliance was 78% ($n = 130$) in group A vs. 82% ($n = 131$) in group B, ($p = 0.41$).

Secondary endpoint: survival, stroke rate and coronary angiography/PCI complications

The combined death and stroke rate at 30 days was 0.5% in group A and 1.8% in group B ($p = .36$). After a median follow up of 6.2 years, 11 deaths occurred in group A (7 related to cancer, 1 to trauma, 2 to lung disease, and 1 of unknown cause), and 24 deaths in group B (6 related to MI, 14 to cancer, 3 to end-stage renal disease, and 1 to lung disease). Among the six deaths due to MI, post mortem confirmation of the diagnosis was available for four. Survival at 6.1 years was 95.6 ± 3.2% in group A and 89.7 ± 3.7% in group B (Fig. 3). Kaplan—Meier estimates were used to generate survival curves and demonstrated higher survival in group A than in group B (log-rank; chi-square: 6.35, $p = .01$). Mortality specifically related to MI was also significantly higher in group B ($n = 6/210$) than in group A ($n = 0/216$) ($p = .01$). No late stroke, either ischaemic or hemorrhagic, was observed during follow up in either group. No complication related to coronary angiography or PCI, such as post-procedural MI or arterial access complication or bleeding due to dual antiplatelet treatment, either post-PCI or post-CEA, occurred during the study period. No antiplatelet treatment related gastrointestinal bleeding was observed or reported either post-operatively or during follow up.

Table 3. Factors associated with cardiac ischemic events. Results of Cox proportional hazard model.[a]

	B	SE	Wald test	*p*	Hazard ratio	Hazard ratio (95% CI)
Coronary angiography vs. none	−2.550	0.607	17.698	<.001	0.078	0.024—0.256
Age <70 years vs. age ≥70 years	1.393	0.349	15.896	<.001	4.025	2.030—7.982
Diabetes vs. none	1.051	0.343	9.360	.002	2.859	1.459—5.605
Female vs. male	−0.025	0.368	0.005	.946	0.975	0.474—2.008
Hyperlipidemia vs. none	0.086	0.399	0.046	.830	0.918	0.420—2.005
Cerebrovascular event vs. none	0.047	0.374	0.016	.899	1.049	0.504—2.182
Hypertension vs. none	0.253	0.454	0.310	.578	1.287	0.529—3.132
PAOD vs. none	0.406	0.501	0.656	.418	1.501	0.562—4.008
Smoking history vs. none	0.332	0.340	0.953	.329	1.393	0.716—2.710

Note. Cerebrovascular event is any transient ischemic attack or any stroke; B = the regression coefficient; PAOD = peripheral occlusive arterial disease; CI = confidence interval; SE = standard error of B.

[a] Cox proportional hazard model: Cardiac ischemic event (MI) serves as the dependent variable; a time variable assesses the duration of the event defined by the dependent variable and covariates (independent categorical variables) with one level being used as reference category. As part of the logistic regression model provided by SPSS, the Omnibus tests of model coefficients leads off with a −2 log likelihood value of 431.10 and a chi-square value of 60.31, which is statistically significant ($p < .001$), indicating that this group of nine covariates significantly affects the probability of occurrence of MI. Among all the covariates that were analyzed in this model, pre-operative coronary angiography was the only variable to significantly decrease the risk of MI with a HR of 0.078. Two covariates, age < 70 years and diabetes significantly increase this risk.

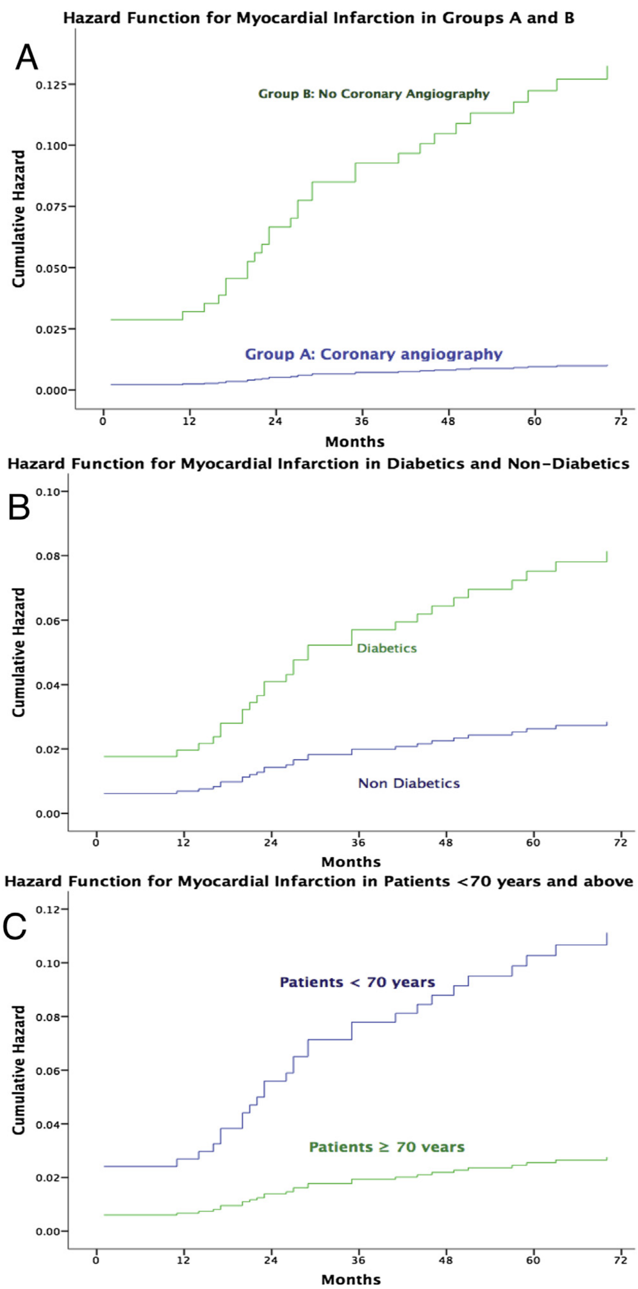


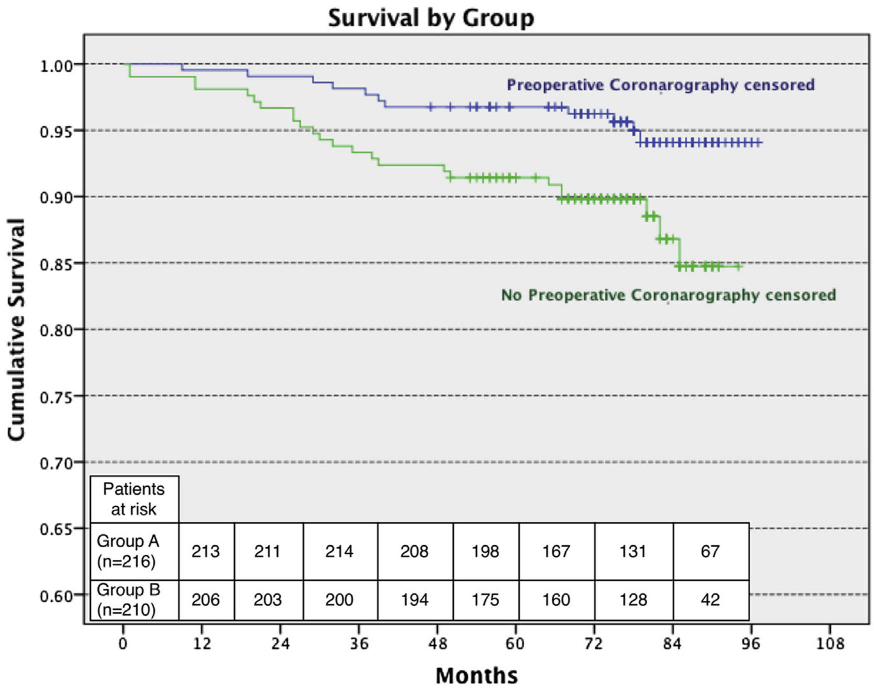
Figure 2. A Cox regression model was used to analyze subgroups of patients with characteristics indicating a high risk of myocardial infarction. It showed that coronary artery angiography followed eventually by coronary revascularization prior to CEA (A) did impart a survival benefit to the patients (HR, .078; 95% CI, 0.024—0.256; $p < .001$) compared with those operated on without coronary angiography. In addition, patients with diabetes (B) presented with an increased risk of MI with an HR of 2.86 (95% CI, 1.46—5.60; $p = .002$) as patients < 70 years (C) with an HR of 4.02 (95% CI, 2.03—7.98; $p < .001$). CEA = carotid endarterectomy; HR = hazard ratio; MI = myocardial infarction.

DISCUSSION

The present study presents an aggressive strategy of prophylactic coronary angiography for patients who are candidates for CEA and suggests that systematic coronary angiography prior to CEA, followed by selective PCI or CABG, significantly lowers the occurrence of late MI and improves late survival. As previously stated, there exist disparate opinions regarding indications for coronary revascularization before elective vascular surgery.[10,20] A comprehensive study of patients having undergone routine coronary angiography before major vascular surgery showed that 60% of these patients have one or more coronary arteries with > 70% stenosis, including 18% with severe triple vessel disease and 4% with left main disease.[8] A recent study found that the prevalence of significant coronary artery disease was 56.8% in vascular surgery patients without cardiac complaints.[21] However, systematic pre-operative coronary angiography followed by selective CABG prior to major vascular surgery is not free from potential complications, and raises risk—benefit issues. While the CARP trial[20] and the DECREASE-V study[22] found no benefit of pre-operative coronary revascularization over medical therapy before vascular surgery, they had some significant limitations.

The CARP trial[3,20] screened 5,859 vascular surgery patients but randomized only 8.9% of them excluding those with left main coronary artery disease. A re-analysis of the trial found that patients who received complete coronary revascularization had fewer post-operative MIs than those who did not.[23] In addition, pre-operative coronary revascularization improved survival in patients presenting with left main coronary artery stenosis (4.6%). In the CARP study, however, this population was excluded from randomization.[24] The DECREASE-V trial[22] randomized 101 vascular surgery patients with severe CAD. In the revascularization arm of this study, 100% of patients had a history of MI and 47% had congestive heart failure. Post-operative mortality reached 22% despite coronary revascularization. The population consisted of patients with multiple small vessel disease who were clearly too ill for CABG or who presented with lesions not amenable to percutaneous coronary artery revascularization. Furthermore, following DECREASE-V investigation, not a single case record form could be found for the 101 patients, and subsequent DECREASE studies fell short of the standards routinely assumed by clinical readers.[25] The American Heart Association/American College of Cardiology guidelines published in 2002[9] recommended coronary angiography only when, after positive non invasive testing, a patient was considered at risk of peri-operative cardiac complications. Recently, however, Monaco et al.[26] demonstrated that a strategy of routine pre-operative coronary angiography followed by selective coronary revascularization provided better survival and cardiovascular event free survival for vascular surgery patients than a strategy of revascularization implemented only after positive non-invasive testing. In addition, the strategy of systematic coronary angiography for patients at medium risk who are candidates for vascular surgery could translate into more effective long-term secondary prevention of coronary events with better adherence to lifelong medical therapy.[27]

Previous studies have shown substantial improvement in long-term survival in patients undergoing vascular surgery



Patients at risk								
Group A (n=216)	213	211	214	208	198	167	131	67
Group B (n=210)	206	203	200	194	175	160	128	42

Figure 3. Long-term survival among patients assigned to undergo coronary artery angiography (group A) or no coronary artery angiography (group B) before carotid endarterectomy. Kaplan—Meier estimates were used to generate survival curves from the time of randomization for all study patients. The median survival was 6.2 years (95% CI, 6.1—6.3 years). Survival at 6 years was 95.6 $\pm$ 3.2% in group A and 89.7 $\pm$ 3.7% in group B, log-rank (chi-square: 6.35, $p = .01$).

where pre-operative thallium scanning is followed by selective coronary angiography and revascularization.[28] However, thallium scanning may not be fully reliable as a predictor of asymptomatic significant coronary artery disease, especially in patients with left main or three vessel disease who are most at risk of post-operative and long-term MI.[29] In a recent prospective study of coronary artery atherosclerosis, the incidence of new coronary ischaemic events from non-significant coronary artery stenoses was 11.6% at 3.4 years,[19] a rate similar to the one observed in group B. Frequently angiographically mild lesions were thin-cap fibroatheromas or were characterized by a large plaque burden, a small luminal area, or some combination of these characteristics, as determined by intravascular ultrasonography.

In the present study, the relatively high incidence of perioperative MI in group B (4.2%) can be explained by the close monitoring of ECG and serum troponin levels for the purposes of the trial, which allowed all subclinical MIs to be detected. The study demonstrates that the strategy of prophylactic coronary angiography for patients who are candidates for CEA not only leads to a significant reduction of post-operative MI, but also favorably impacts the natural history of coronary atherosclerosis by reducing the rate of late ischemic events. Overall, this finding underscores the impact of post-operative MI on short- and long-term survival after vascular surgery.[30,31]

One concern in this study was that coronary artery angiography might lead to overtreatment of coronary artery lesions and unduly expose asymptomatic patients to complications related to an invasive procedure. In this series, however, no myocardial infarction was observed as a consequence of coronary angiography or revascularization and the mild increase of cardiac biomarkers observed after PCI, without clinical symptoms and/or ECG alterations, has been shown not to be associated with an increased risk of death and MI.[32] Furthermore, no post-operative or late bleeding related to dual antiplatelet treatment was noted in this study. And yet, despite these favorable results, the use of both CEA and PCI/CABG in an asymptomatic patient above 75 years of age may appear unjustified and prohibitively costly. However, in line with the 10 year results of the Asymptomatic Carotid Surgery Trial,[33,34] pre-operative coronary angiography followed by optional PCI/CABG could further reduce perioperative and late MI including fatal ones as shown in this study, helping to ensure better life expectancy and allowing older patients with severe asymptomatic carotid artery stenosis to benefit from CEA for many years, thereby justifying the additional costs associated with this policy.

In order to find variables that could help to identify subgroups of patients with severe carotid stenosis who would be at higher risk of significant asymptomatic CAD, risk factors were entered in a Cox proportional hazards regression, which demonstrated that diabetes and age < 70 years were associated with a higher risk of asymptomatic CAD. As this subset of patients would be most likely to benefit from systematic pre-operative coronary angiography, in the interests of cost-effectiveness it is suggested that pre-operative coronary artery imaging should be limited to them.

The use of a less invasive test such as pre-operative thallium scanning or coronary CT-scan instead of coronary angiography has also been considered. However, as shown by Bursi et al.[35] these investigations may not to be as effective as standard coronary angiography as a means of recognizing significant CAD in asymptomatic patients. Moreover, Back et al.[36] have demonstrated that the presence of three vessel angiographic CAD was an independent predictor of cardiac morbidity, whereas induced ischemia by test imaging was not. Furthermore, among elderly people, a negative and/or equivocal non-invasive stress test does not necessarily exclude appreciable CAD involvement.[37]

Despite the potential impact of this study, some of its limitations should be emphasized. First, the group receiving coronary angiography and subsequent coronary revascularization had a very low rate of complications. Secondly, the rate of drug compliance exceeding 80% at 6 years for statins, and dual antiplatelet regimes could limit the applicability of the results in usual practice where higher surgical risk and lower drug compliance is commonly reported. In addition, generalization of these results should be limited to patients with severe carotid stenosis undergoing surgery. Finally, as the patients were unblinded, awareness of the treatment assignment may have led to possible bias concerning the diagnoses of potential MI occurring during follow up that, except for post mortem examination, were given by the cardiologists in charge of the patients and not by independent observers. However, outcomes were objectively assessed by all authors and analysis of the data suggests no group difference in appropriateness of care or reliability of the results.

CONCLUSIONS

This RCT has shown that systematic coronary angiography followed by selective coronary revascularization before CEA in patients with asymptomatic coronary artery disease was safe and could improve long-term freedom from MI and late survival. These findings from a relatively small RCT need to be confirmed by additional larger controlled studies. In addition, considering the potential risk of MI in these patients but also the opportunity cost, a possibly less invasive screening test with pre-operative thallium scanning or coronary CT should be investigated.

FUNDING

This study was supported by a research grant (Prot.P 187/07) from the University of Roma “La Sapienza”.

CONFLICT OF INTEREST

None.

ACKNOWLEDGEMENTS

The authors acknowledge the assistance of Mr Jeffrey Robert Arsham with language editing of the article.

REFERENCES

1 Sukhija R, Aronow WS, Yalamanchili K, Sinha N, Babu S. Prevalence of coronary artery disease, lower extremity peripheral arterial disease, and cerebrovascular disease in 110 men with an abdominal aortic aneurysm. *Am J Cardiol* 2004;**94**:1358–9.
2 Dieter RS, Tomasson J, Gudjonsson T, Brown RL, Vitcenda M, Einerson J, et al. Lower extremity peripheral arterial disease in hospitalized patients with coronary artery disease. *Vasc Med* 2003;**8**:233–6.
3 McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, et al. Coronary artery revascularization before elective major vascular surgery. *N Engl J Med* 2004;**351**:2795–804.
4 Roger VL, Ballard DJ, Hallett Jr JW, Osmundson PJ, Puetz PA, Gersh BJ. Influence of coronary artery disease on morbidity and mortality after abdominal aortic aneurysmectomy: a population-based study, 1971–1987. *J Am Coll Cardiol* 1989;**14**:1245–52.
5 Hollier LH, Plate G, O’Brien PC, Kazmier FJ, Gloviczki P, Pairolero PC, et al. Late survival after abdominal aortic aneurysm repair: Influence of coronary artery disease. *J Vasc Surg* 1984;**1**:290–9.
6 McFalls EO, Ward HB, Santilli S, Scheftel M, Chesler E, Doliszny K. The influence of peri-operative myocardial infarction on long-term prognosis following elective vascular surgery. *Chest* 1998;**113**:681–6.
7 Jamieson WR, Janusz MT, Miyagishima RT, Gerein AN. Influence of ischaemic heart disease on early and late mortality after surgery for peripheral occlusive vascular disease. *Circulation* 1982;**66**:192–7.
8 Hertzer NR, Beven EG, Young JR, O’Hara PJ, Ruschhaupt 3rd WF, Graor RA, et al. Coronary artery disease in peripheral vascular patients: a classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984;**199**:223–33.
9 Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery-executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Anesth Analg* 2002;**94**(5):1052–64.
10 Pierpont GL, Moritz TE, Goldman S, Krupski WC, Littooy F, Ward HB, et al. Disparate opinions regarding indications for coronary artery revascularization before elective vascular surgery. *Am J Cardiol* 2004;**94**:1124–8.
11 Gottlieb A, Banoub M, Sprung J, Levy PJ, Beven M, Mascha EJ. Post-operative cardiovascular morbidity in patients with coronary artery disease underscoring vascular surgery after percutaneous transluminal coronary angioplasty. *J Cardiothorac Vasc Anesth* 1998;**12**:501–6.
12 Brilakis ES, Orford JL, Fasseas P, Wilson SH, Melby S, Lennon RJ, et al. Outcome of patients undergoing balloon angioplasty in the two months prior to non-cardiac surgery. *Am J Cardiol* 2005;**96**:512–4.
13 Rihal CS, Eagle KA, Mickel MC, Foster ED, Sopko G, Gersh BJ. Surgical therapy for coronary artery disease among patients with combined coronary artery and peripheral vascular disease. *Circulation* 1995;**91**:46–53.
14 Abir F, Kakisis I, Sumpio B. Do vascular surgery patients need a cardiology workup? A review of pre-operative cardiac clearance guidelines in vascular surgery. *Eur J Vasc Endovasc Surg* 2003;**25**:110–7.
15 Back MR, Stordahl N, Cuthbertson D, Johnson BL, Bandyk DF. Limitations in the cardiac risk reduction provided by coronary revascularization prior to elective vascular surgery. *J Vasc Surg* 2002;**36**:526–33.

16 Goessens BM, Visseren FL, Algra A, Banga JD, Van Der Graaf Y. Screening for asymptomatic cardiovascular disease with non invasive imaging in patients at high risk and low risk according to the European guidelines on cardiovascular disease prevention: the SMART study. *J Vasc Surg* 2006;**43**:525—32.
17 Illuminati G, Ricco J-B, Greco C, Mangieri E, Calio' F, Ceccanei G, et al. Systematic pre-operative coronary angiography and stenting improves post-operative results of carotid endarterectomy in patients with asymptomatic coronary artery disease: a randomised controlled trial. *Eur J Vasc Endovasc Surg* 2010;**39**:139—45.
18 North American Symptomatic Carotid Endarterectomy Trial (NASCET) Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade carotid stenosis. *N Eng J Med* 1991;**325**:445—53.
19 Stone GW, Maehara A, Lansky AJ, De Bruyne B, Cristea E, Mintz GS, et al. PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;**364**:226—35.
20 Raghunathan A, Rapp JH, Littooy F, Santilli S, Krupski WC, Ward HB, et al. Post-operative outcomes for patients undergoing elective revascularization for critical ischaemia and intermittent claudication: a subanalysis of the coronary artery revascularization prophylaxis (CARP) trial. *J Vasc Surg* 2006;**43**: 1175—82.
21 den Dekker MA, van den Dungen JJ, Tielliu IF, Jaspers MM, Oudkerk M, Vliegenthart R. Prevalence of severe subclinical coronary artery disease on cardiac CT and MRI in patients with extra-cardiac arterial disease. *Eur J Vasc Endovasc Surg* 2013;**46**:680—9.
22 Poldermans D, Schouten O, Vidakovic R, Bax JJ, Thomson IR, Hoeks SE, et al. A clinical randomized trial to evaluate the safety of a non invasive approach in high risk patients undergoing major vascular surgery. The DECREASE-V pilot study. *J Am Coll Cardiol* 2007;**49**:1763—9.
23 Ward HB, Kelly RF, Thottapurathu L, Moritz TE, Larsen GC, Pierpont G, et al. Coronary artery bypass grafting is superior to percutaneous coronary intervention in prevention of perioperative myocardial infarctions during subsequent vascular surgery. *Ann Thorac Surg* 2006;**82**:795—801.
24 Garcia S, Moritz TE, Ward HB, Pierpont G, Goldman S, Larsen GC, et al. Usefulness of revascularization of patients with multivessel coronary artery disease before elective vascular surgery for abdominal aortic and peripheral occlusive disease. *Am J Cardiol* 2008;**102**:809—13.
25 Bouri S, Shun-Shin MJ, Cole GD, Mayet J, Francis DP. Meta-analysis of secure randomised controlled trials of beta blockade to prevent peri-operative death in non-cardiac surgery. *Heart* 2014;**100**:456—64.
26 Monaco M, Stassano P, Di Tommaso L, Pepino P, Giordano A, Pinna GB, et al. Systematic strategy of prophylactic coronary angiography improves long-term outcome after major vascular surgery in medium to high risk patients: a prospective randomized study. *J Am Coll Cardiol* 2009;**8**:989—96.
27 Landesberg G, Mosseri M. Prophylactic pre-operative coronary revascularization. Is the Phoenix awakening? *J Am Coll Cardiol* 2009;**54**:997—8.
28 Landesberg G, Mosseri M, Wolf YG, Bocher M, Basevotch A, Rudis E, et al. Pre-operative thallium scanning, selective coronary revascularization, and long-term survival after major vascular surgery. *Circulation* 2003;**108**:177—83.
29 Chung SY, Lee KY, Chun EJ, Lee WW, Park EK, Chang HJ, et al. Comparison of stress perfusion MRI and SPECT for detection of myocardial ischaemia in patients with angiographically proven three-vessel coronary artery disease. *AJR Am J Roentgenol* 2010;**195**:356—62.
30 van Waes J, Nathoe HM, de Graaff JC, Kemperman H, de Borst GJ, Peelen LM, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* 2013;**127**:2264—71.
31 Simons JP, Baril DT, Goodney PP, Bertges DJ, Robinson WP, Cronenwett JL, et al. The effect of post-operative myocardial ischaemia on long-term survival after vascular surgery. *J Vasc Surg* 2013;**58**:1600—8.
32 Prasad A, Gersh BJ, Bertrand ME, Lincoff AM, Moses JW, Ohman EM, et al. Prognostic significance of periprocedural versus spontaneously occurring myocardial infarction after percutaneous coronary intervention in patients with acute coronary syndromes: an analysis from the ACUITY trial. *J Am Coll Cardiol* 2009;**54**:477—86.
33 Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;**363**(9420): 1491—502.
34 Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al. Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet* 2010 25;**376**(9746):1074—84.
35 Bursi F, Babuin L, Barbieri A, Politi L, Zennaro M, Grimaldi T, et al. Vascular surgery patients; peri-operative and long-term risk according to the ACC/AHA guidelines, the additive role of post-operative troponin elevation. *Eur Heart J* 2005;**26**:2448—56.
36 Back MR, Schmacht DC, Bowser AN, Stordahl N, Cuthbertson D, Johnson BL, et al. Critical appraisal of cardiac risk stratification before elective vascular surgery. *Vasc Endovasc Surg* 2003;**37**: 387—97.
37 Psirropoulos D, Efthimiadis A, Boudonas G, Papadopoulos I, Papadopoulos G, Ekklisiarchos D, et al. Detection of myocardial ischemia in the elderly versus the young by stress thallium-201 scintigraphy and its relation to important coronary artery disease. *Heart Vessels* 2002;**16**:131—6.